UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,338	07/11/2003	Jin-an Jiao	TNA-005.04	8452

25226 7590 06/19/2008
MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
XIE, XIAOZHEN	
ART UNIT	**PAPER NUMBER**
1646	
MAIL DATE	**DELIVERY MODE**
06/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/618,338	JIAO ET AL.	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,39-46,54-60,65 and 69-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39-46,54-60,65 and 69-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070911, 20080306*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The Information Disclosure Statements (IDS) filed on 11 September 2007 and 6 March 2008 have been entered. Applicant's amendment of the claims filed on 6 March 2008 has been entered.

Claims 1-36, 38, 47-53, 61-64 and 66-68 are cancelled. Claims 69-82 have been added. Claims 37, 39-46 and 54-60, 65 and 69-82 are pending and under examination.

Claim Rejections Withdrawn

The rejection of claims 37 under 35 U.S.C. 112, second paragraph, as being indefinite for reciting "a sequence represented by SEQ ID NO: 2 or SEQ ID NO: 4", wherein the metes and bounds of the term "represented by" cannot be determined, is withdrawn in response to Applicant's amendment of the claims.

The rejection of claims 45 under 35 U.S.C. 112, second paragraph, as being indefinite for lacking an antecedent basis for the limitation of "the humanized antibody" in claim 37, is withdrawn in response to Applicant's amendment of the claims.

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The amended and newly added claims 37, 39-46, 54-60, 65, 69-71 and 73-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: *a method for reducing tissue factor (TF) levels to treat a solid tumor exhibiting TF expression, comprising administering to a mammal having the tumor a therapeutically effective amount of an antibody that comprises the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4, or fragment thereof that binds native human tissue factor to form a complex, whereby Factor X binding to the complex is inhibited, and Factor VII or VIIa binding to tissue factor is not inhibited,* does not reasonably provide enablement for administering variants of SEQ ID NO: 2 or 4, nor for prophylactic treatment (i.e., administering to any mammal), for reasons set forth in the previous office actions.

Applicant argues that the claims, as amended, now recite a method for reducing tissue factor levels to treat a tumor exhibiting tissue factor expression. Applicant argues that the claim amendment has obviated the rejection for lack of enablement.

Applicant's arguments have been fully considered but have not been found to be persuasive.

Independent claim 37 still recites "comprising administering to a mammal a therapeutically effective amount of an antibody". The claim language does not limit patient population. In other word, the claims encompass administering the antibody to any mammal, including one without the tumor. As set forth previously, Applicant has not provided support for treatment of any mammal or prophylactic treatment. Applicant has not provided support that prophylaxis can be achieved without adverse effects in normal

individuals. Without detailed guidance, the artisan would not be able to predict the outcome of the prophylactic treatment using the claimed antibody. Amending the claim to recite "a mammal having the tumor" would obviate the rejection.

In addition, the newly added claims 69-71 and 73-82 recite administering an anti-TF antibody derived from the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4. The claim language read on the use of variants of SEQ ID NO:2 or 4, and such variant antibodies exhibit the properties of forming a complex with native tissue factor, whereby Factor X binding to the complex is inhibited and Factor VII or VIIa binding to TF is not inhibited. As discussed in the Office action mailed on June 14, 2006, the specification does not provide sufficient guidance for making these variant antibodies possessing the recited properties. Without teachings in the specification regarding the structures or data supporting the claims drawn to variants or fragments of the antibody, one of ordinary skill in the art would not know how to use the invention commensurate in scope with the claims.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 69 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not provide support for the invention as now claimed: "an anti-tissue factor antibody derived from the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4, or fragment thereof". Applicant's amendment, filed 6 March 2008, asserts that no new matter has been added and directs support for the newly added claims at various sections of the instant specification (paragraphs [0044] [0046-0049], and Examples). However, the instant specification as filed does not provide sufficient written description for the limitation of "an anti-tissue factor antibody derived from the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4, or fragment thereof". This is a new matter rejection.

Applicant is required to cancel the new matter in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06.

In addition, Claims 69-71 and 73-82 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method for inhibiting tissue factor (TF) activity to treat a tumor exhibiting TF expression, comprising administering an anti-TF antibody derived from the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4, or fragment

thereof that binds native human tissue factor to form a complex, whereby Factor X binding to the complex is inhibited and Factor VII or VIIa binding to TF is not inhibited. The claim language encompasses anti-TF antibodies comprising variants of SEQ ID NO:2 or 4, and such variant antibodies exhibit the recited properties. As discussed in the Office Action mailed on June 14, 2006, the specification has described an anti-TF antibody H36.D2.B7 [ATCC HB12255], or an anti-TF antibody comprising the amino acid sequence set forth in SEQ ID NO: 2 or 4. The specification does not provide adequate written description for the full scope of the claimed antibody variants or fragments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 69, 71 and 75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 69 recites "an anti-tissue factor antibody derived from the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4, or fragment thereof". The term "derived from" is not defined in the specification, and the skilled artisan cannot determine the metes and bounds of the term. For example, it is unclear if the claim language requires any particular structural characteristics.

Claim 71 recites "identifying characteristics of H36.D2.B7 deposited as ATCC HB-12255". It is unclear and indefinite what the identifying characteristics are.

Claim 75 recites the limitation "wherein the chimeric antibody" in claim 69. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 69, 73 and 78-82 are rejected under 35 U.S.C. 102(b) as being anticipated by Edgington et al. (U. S. Patent NO: 5,223,427, issued on 29 June 1993, reference provided previously).

The instant claims are directed to a method for inhibiting tissue factor activity to treat a tumor exhibiting tissue factor expression, comprising administering to a mammal (e.g., a human) having the tumor a therapeutically effective amount of an anti-tissue factor antibody (e.g., a monoclonal antibody) derived from the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO:4, or fragment thereof that binds native human tissue factor to form a complex, whereby Factor X binding to the complex is inhibited and Factor VII or VIIa binding to tissue factor is not inhibited (claims 69, 73, 82), wherein the tissue factor activity is inhibited by at least about 50%, 80%, 90% or 95% (claims 78-81).

The ‘427 patent teaches a method of treating a human patient having tumor cells, e.g., breast and lung carcinoma, that express tissue factor (TF) on their cell surface, by

administering to the patient an anti-TF monoclonal antibody (MoAb) linked to an anti-tumor agent to form an anti-tumor therapeutic composition (col. 23, lines 3-11). The '427 patent teaches that the anti-TF MoAbs include anticoagulant (neutralizing) MoAb or non-neutralizing MoAb, which immunoreact with human TF (to form a complex) (col. 21, lines 18-41). The '427 patent teaches an neutralizing anti-TF MoAb, TF8-11D12, which was further characterized by Fiore et al. (Blood, 1992, Vol. 80(12):3127-3134, reference provided previously), as being not to block Factor VIIa binding to TF, but specifically blocking access of Factor X to the formed complex of TF and Factor VIIa (pp. 3127, Abstract, and last paragraph in Introduction). Fiore et al. further showed that TF8-11D12 inhibits Factor IX and Factor X activation by at least 95% (pp.3131, Fig. 4). Given the indefinite nature of the claims as written (see rejection under 35 USC §112 second paragraph, supra), the anti-TF MoAb taught by the '427 patent meets the limitation of the instant claims. Therefore, the '427 patent anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 74-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Edgington et al. (U. S. Patent NO: 5,223,427), in view of Queen et al. (U. S. Patent NO: 5,693,762, issued on 2 December 1997, reference provided previously).

The '427 patent teaches as set forth above. The '427 patent, however, does not teach that the antibody is a chimeric antibody that comprises a constant region of human origin (claims 74, 75), a humanized antibody that comprises at least one hypervariable regions of non-human origin (claim 76), or a single chain antibody (claim 77).

The '762 patent teaches chimeric and humanized antibodies that have mouse variable regions joined to human constant regions. The '762 patent teaches that humanized antibodies are important because they bind to the same antigen as the original antibodies, but are less immunogenic when injected into humans(col. 1, line 56 bridging col. 2, line 9). (col. 2, lines 6-9). The '762 patent further teaches making a single chain antibody (col. 17, line 32-61).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the '427 patent, with those of the '762 patent, to generate the humanized or chimeric anti-TF antibody, or the single chain anti-TF antibody. One of ordinary skill in the art would have been motivated to combine the teachings, because the '427 patent teaches an anti-TF MoAb that can be used for treating a tumor, and the '762 patent teaches modifying monoclonal antibodies for human therapeutic uses. Therefore, the combined teachings provide a reasonable expectation of successfully treating tumors that express TF on cell surface.

Conclusion

NO CLAIM IS ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
June 12, 2008

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646